# Cardiac Resynchronization Therapy: a New Frontier in the Management of Heart Failure

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The prevalence of heart failure has risen dramatically in the last decade [1], reaching epidemic proportions. A significant proportion of heart failure patients have rhythm and conduction abnormalities that adversely affect cardiac performance [2]. Implanted devices with cardiac resynchronization therapy capabilities can reverse atrioventricular and intraventricular conduction abnormalities, and treat both brady and tachyarrhythmias. Recent studies demonstrate significant improvement in hemodynamic parameters, functional capacity and quality of life in selected heart failure patients treated with CRT [3–11]. Based on these results, the U.S. Food and Drug Administration has recently approved the use of CRT for patients with reduced systolic function, drug-refractory heart failure symptoms, and conduction abnormalities. This review summarizes the current data on CRT and points to future directions in electrical therapy of heart failure.

## Hemodynamic effects of cardiac resynchronization

Biventricular pacing was first reported 20 years ago by De Teresa and Chamoro [12] who described its beneficial effects in four patients. Since then, several acute studies have confirmed the role of CRT in improving hemodynamic indices in patients with systolic heart failure and conduction abnormalities [13–18]. Studies using invasive hemodynamic measurements demonstrate that biventricular pacing is associated with a 28–35% increase in cardiac index [13,15], a 16–30% reduction of precapillary pulmonary wedge pressure [13–15], and a 7% elevation in systolic blood pressure [14]. Interestingly, several acute studies observed a more prominent effect on dp/dt by left ventricular-only pacing [17,18] reaching 15–43%, compared to 13–14% when BV pacing was used [17]. The change in pulse pressure was also more prominent with LV pacing alone measuring 7.5–19% [17,18], compared to an improvement of 6.5–15% with BV pacing [17]. A clinical study, however, did not find a significant difference in the effects of either LV only or BV pacing in patients with heart failure [3]. Several studies, including BELIEVE, PAVE and OPTSITE, are currently being planned in order to clarify this question. While existing studies implemented simultaneous right ventricular and LV pacing, this mode might not be the optimal one for heart failure patients. Newer devices capable of separating RV and LV sensing and pacing are expected to further optimize the hemodynamic effects of CRT [19].

Benefits of CRT can also be demonstrated using non-invasive methods. Breithardt et al. [20] used Doppler echocardiography to evaluate the effects of RV, LV, or BV pacing in 32 patients with heart failure and intraventricular conduction abnormalities. Both LV and BV stimulation resulted in a significant improvement of LV filling time, aortic velocity time integral, and myocardial performance index. No significant effect on diastolic function was noted with either LV or BV pacing.

Although essential for understanding the mechanisms of CRT beneficial effects, acute hemodynamic studies have important limitations. Most of these studies were performed with patients in the supine position under sedation or general anesthesia, some of whom even had open chest during heart surgery [16]. The hemodynamic mechanisms operating under these circumstances are completely different from those responsible for effort-induced symptoms in heart failure patients. In addition, some of the acute hemodynamic studies implemented epicardial pacing [15–17], resulting in a myocardial activation sequence that is distinctly different from that achieved by chronic endocardial pacing. The next section will describe the available clinical data regarding chronic CRT.

## Clinical effects of CRT

To date, over 16,400 BV pacemaker units and 4,500 BV implantable cardioverter defibrillators have been implanted worldwide [personal communications: Medtronic Inc. St Paul, MN, USA and CPI/Guidant Inc. St Paul, MN], and results from several clinical studies together

CRT = cardiac resynchronization therapy
BV = biventricular
LV = left ventricular
RV = right ventricular

**Table 1.** Completed clinical trials of biventricular pacing for patients with severe heart failure

| Study [ref] | No. of patients | Inclusion criteria | Endpoints | Results with BV pacing |
|---|---|---|---|---|
| PATH-CHF [3] | 42 | NYHA II-IV, QRS>120 ms, sinus rate > 55 bpm | NYHA class, QOL, 6 min walk, peak $VO_2$, AT, hospitalization | Improvement in NYHA functional class and QOL |
| InSync [22] | 103 | NYHA III-IV, LVEF ⩽ 0.35, LVEDD ⩾ 60 mm, QRS ⩾ 150 ms | NYHA class, QOL, 6 min walk, QRS width | Improvement in NYHA functional class, 6 min walk, and QOL |
| MUSTIC [5] | 131 | NYHA III, LVEF < 0.35, LVEDD > 60 mm, QRS >150 ms, 6 min walk < 450 m | QOL, 6 min walk, peak $VO_2$, hospitalization | Improvement in 6 min walk, QOL, and peak $VO_2$. Reduction in hospitalization rate |
| MIRACLE [23] | 453 | NYHA III-IV, LVEF ⩽ 0.35, LVEDD ⩾ 55 mm, QRS ⩾ 130 ms, stable HF medication regimen for > 3 months. No pacing indication. | NYHA class, QOL, 6 min walk, peak $VO_2$, hospitalization, neurohormone levels, echo indices, mortality | Improvement in NYHA functional class, 6 min walk, QOL, LVEF, LV volumes, and MR |
| InSync ICD [4] | 81 | NYHA II-IV, LVEF ⩽ 0.35, LVEDD ⩾ 55 mm, QRS ⩾ 130 ms, an ICD indication. | Safety and effectiveness of combining ICD with BV pacing, NYHA class, QOL, 6 min walk | Safe to combine ICD + BV pacing. Improvement in NYHA functional class only in patients with baseline NYHA III or IV |
| CONTAK CD [33] | 490 | NYHA II-IV, LVEF < 0.35, QRS > 120 ms, normal sinus node, ICD indication | Safety and effectiveness of combining ICD + CRT, NYHA class, QOL, peak $VO_2$, 6 min walk | Safe to combine ICD + BV pacing. Improvement in peak $VO_2$, and in QOL in patients with baseline NYHA III-IV without RBBB |

QOL = quality of life, $VO_2$ = oxygen consumption, AT = anaerobic threshold, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end-diastolic diameter, HF = heart failure, LV = left ventricle, MR = mitral regurgitation, ICD = implantable cardioverter defibrillator, RBBB = right bundle branch block.

involving more than 1,300 patients are available [Table 1]. Earlier studies [6–8,13] indicated an improvement in quality of life, 6 minute walk test, and New York Heart Association functional class in patients with heart failure treated with CRT. These studies were non-randomized and lack a placebo control arm.

PATH-CHF (Pacing Therapies for Congestive Heart Failure) was the first randomized study [3]. In this controlled trial 42 patients in sinus rhythm with NYHA functional class III or IV, PR interval ⩾ 150 msec, and QRS width ⩾ 120 msec were randomized to RV, LV, or BV pacing in the VDD mode at one of five atrioventricular delays. LV pacing was performed using an epicardial approach. Acute invasive hemodynamic measurements were performed at implantation, and patients were paced at the optimized mode for the first month. During the second month no pacing was implemented, and in the third month patients were paced at the non-optimal mode. An increase in maximal oxygen consumption was observed during the first and third months, but not during the second inactive phase. During the fourth to sixth months, patients were again paced in the optimized mode. An echocardiographic evaluation was performed in 25 of these patients 6 months after implantation. When compared with values prior to implantation, left ventricular end-systolic and end-diastolic diameters as well as volumes were significantly reduced, and the ejection fraction increased at 6 months. Of interest, patients who did not respond favorably to LV or BV pacing were those with the highest LV end-diastolic volumes pre-implant. Recently, the authors of PATH-CHF reported an echocardiographic analysis of 34 patients [21] with quantification of LV asynchrony before and during CRT. According to their findings, patients with LV asynchrony at baseline were more likely to have improved systolic function with CRT. The InSync study was the first to use transvenous leads for LV pacing. Initial results [22] indicate an improvement in NYHA functional class, quality of life, and 6 minute walk with BV pacing compared to baseline. This study, however, was not randomized or placebo-controlled.

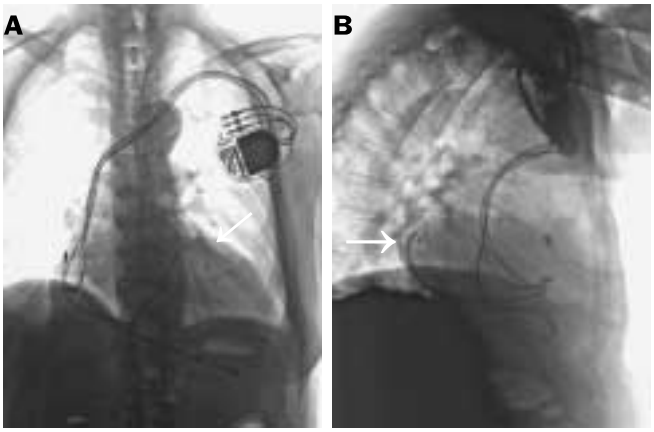


**Figure 1.** A typical chest X-ray showing the postero-anterior **[A]** and lateral views **[B]** of a biventricular pacing system. Arrows point to the lead in coronary sinus. The other two leads are located in the right ventricular apex and right atrial appendage (courtesy of Dr. Daniel Gras).

MUSTIC (Multisite Stimulation in Cardiomyopathies) is the first study that is both randomized and placebo-controlled. The study enrolled 67 patients in normal sinus rhythm [5] and 64 patients with chronic atrial fibrillation after AV node ablation in a crossover design. Two weeks after implantation, patients were randomized to 12 weeks of either BV pacing or no pacing at all, and the mode of

NYHA = New York Heart Association

therapy was switched for the next 12 weeks. A significant improvement in exercise capacity, symptoms, and maximal oxygen consumption was observed only during active pacing. This improvement was maintained over a 12 month follow-up period.

MIRACLE, the Multicenter InSync Randomized Clinical Evaluation study [23], was completed recently. This prospective randomized double-blind controlled study enrolled heart failure patients in sinus rhythm, NYHA functional class III/IV, LV ejection fraction $\leqslant$ 0.35, LV end-diastolic diameter $\geqslant$ 55 mm, QRS duration $\geqslant$ 130 msec, and no pacing indication. All patients were implanted with a cardiac resynchronization system. Patients were randomized to 6 months of CRT (n=228) or to a placebo control arm (n=225). As compared to the control group, patients receiving CRT experienced significant improvement in the 6 minute walk test, functional class, quality of life, exercise capacity, and LV ejection fraction. A reduction in the need for hospitalization and intravenous treatment for heart failure was also observed.

The VIGOR CHF investigators [24] recently reported a significant reduction in left atrial volume, LV end-systolic and end-diastolic dimensions and LV end-systolic volume after 12 weeks of BV pacing in 53 patients with systolic heart failure. In a retrospective report, Auricchio et al. [25] describe a significant improvement in all ventilation and metabolic parameters in 50 patients with heart failure and conduction delays treated with CRT [25]. Patients with more depressed metabolic and ventilation parameters at baseline seemed to benefit most.

### Effects of cardiac resynchronization in patients with chronic atrial fibrillation

While most studies that evaluated the clinical effects of CRT enrolled patients with normal sinus rhythm [3–5,7,23–25], several reports include patients with chronic atrial fibrillation, with or without His bundle ablation. The largest of these reports is the MUSTIC trial [5] with 43 patients in chronic atrial fibrillation after atrioventricular node ablation. These patients experienced significant improvement in all functional parameters with CRT, although the benefit seems to be less than that observed in patients with sinus rhythm. Lupi and co-workers [10] in a smaller study report a significant improvement in ejection fraction and LV velocity integral in patients with sinus rhythm (n=6) or chronic atrial fibrillation (n=7), however the effect on ejection fraction was more pronounced in the group with sinus rhythm.

### The effect of cardiac resynchronization on mortality from heart failure

In the MIRACLE study, no difference in mortality was observed at 6 months between the active CRT group and the placebo group. However, mortality was relatively low (<10%) in both arms [9]. Larger studies aimed to assess the effects of CRT on mortality of patients with advanced heart failure are currently underway. Notably, at this point there are no studies that prove a survival benefit of CRT.

The COMPANION trial (Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure) [26] is intended to recruit 2,200 patients with NYHA class III/IV, ejection fraction $\leqslant$ 0.35, and QRS $\geqslant$ 120 msec in three different arms: CRT only, CRT with ischemic coronary disease, and a placebo control group. The study will determine whether optimal pharmacologic therapy with CRT, or CRT combined with an ICD is superior to optimal pharmacologic therapy alone in reducing combined all-cause mortality and hospitalizations, reducing cardiac morbidity, and improving functional capacity, cardiac performance and quality of life. The study is powered to determine a mortality benefit of 25% in this patient population. Other smaller studies with the purpose of testing the effects of CRT on mortality of patients with heart failure are the CARE-HF and PACMAN trials. CARE-HF will randomize 800 patients to CRT or control for a minimum of 18 months with a primary endpoint of all-cause mortality and cardiac hospitalization [27]. Results of this study are expected in 2004.

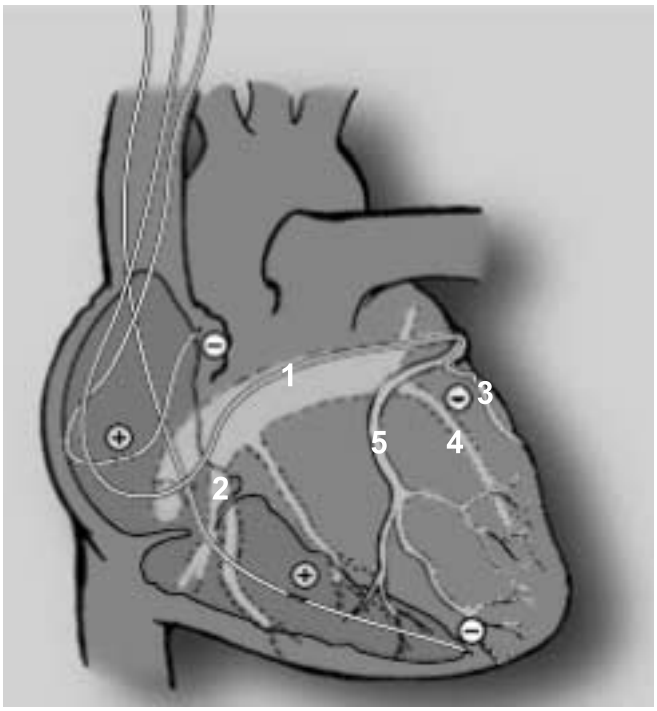


**Figure 2.** Coronary venous anatomy.
1 = coronary sinus, 2 = middle cardiac vein, 3 = lateral cardiac vein, 4 = posterolateral cardiac vein, 5 = great cardiac vein.
*Courtesy Medtronic, Inc.*

### Selecting appropriate candidates

CRT is an invasive and expensive form of therapy for heart failure, and candidates must be very carefully selected to ensure maximal benefit with minimal risk. Based on information gathered so far [3–7,10,11,23–25], it is concluded that patients with significant drug-refractory systolic heart failure who are in sinus rhythm and have a widened QRS complex benefit clinically from CRT in terms of hemodynamic parameters, functional capacity, hospitalization rates, and the quality of life. More studies are needed to clarify whether patients with chronic atrial fibrillation [6,8,10,11] or those with a milder degree of heart failure symptoms can benefit from this form of therapy.

ICD = implantable cardioverter defibrillator

The simplest marker for cardiac dyssynchrony that was widely used to select patients for the above-mentioned trials is the width of the QRS complex [13]. In acute studies patients with wider QRS complexes had a greater mechanical response to CRT [17,28,29]. Most clinical studies of CRT [3,6,28] used a cutoff of $\geqslant$ 120 msec for enrollment. In InSync ICD [4], and in the MIRACLE trial [23] the cutoff was $\geqslant$ 130 msec, and in MUSTIC [5] a QRS width of $\geqslant$ 150 msec was required for enrollment. Interestingly enough, some studies found no correlation between QRS narrowing and a beneficial mechanical systolic effect of BV pacing [17]. This might reflect the fact that QRS width is a somewhat crude estimate of cardiac synchrony.

A more direct and accurate way for assessing cardiac dyssynchrony is magnetic resonance imaging. This method also provided the strongest correlate with clinical response to CRT [30]. Other methods such as radionuclide cineangiograhpy [31], Doppler strain analysis [29], and contrast echocardiography [32] were also used to assess cardiac dyssynchrony. The latter two are particularly appealing, being non-invasive and simple to perform in a clinical setting. Studies are needed to assess which method will best predict which patients are likely to benefit most from CRT.

The other important variable in selecting patients for CRT in conjunction with the degree of cardiac dyssynchrony is the degree of systolic dysfunction. The vast majority of studies [5,6,23,25] enrolled patients with LV ejection fraction of 35% or less, and NYHA class III or IV symptoms. In InSync ICD, which enrolled patients with NYHA functional class II-IV [4], only patients with baseline class III or IV achieved an improvement in functional class with BV pacing. Similar results were obtained in the CONTAK CD trial [33], where only patients with baseline NYHA class III or IV achieved an improvement in quality of life with CRT. In the PATH-CHF study, patients who did not respond to CRT had a significantly higher baseline LV end-diastolic volume [3] of mean 351 ml compared to a mean of 234 ml in responders. It should be noted, however, that only four patients in this study were considered to be non-responders to CRT. Table 2 summarizes the current recommendations for CRT.

## Selecting an optimal LV pacing site

The optimal LV pacing site is not yet determined, and probably varies from patient to patient [34]. In most patients, however, pacing the midlateral or posterior portions of the LV results in a better hemodynamic response than pacing of the anterior or apical LV [34–36]. This is explained by the fact that in patients with left bundle branch block the LV base is the latest to be activated [37]. Pre-stimulation of this area will provide maximal synchronization of the LV, and can also ameliorate systolic mitral insufficiency that results from the late activation of the posterolateral papillary muscle. Pacing the LV from multiple sites was suggested by Pappone et al. [38] and is still investigational.

**Table 2.** Current indications for biventricular pacing

| |
|---|
| Drug-refractory symptomatic heart failure |
| NYHA functional class III or IV |
| LV ejection fraction $\leqslant$ 0.35 |
| QRS duration $\geqslant$ 130 msec with a left bundle branch block morphology |

## Future directives

Although much progress has been achieved in the last few years in our understanding of the pathophysiologic and clinical effects of CRT, many questions remain unanswered. With the release of new devices capable of separating RV and LV sensing and pacing, a whole new spectrum of programming possibilities [19] is being opened, and further improvements in hemodynamics, symptoms, and possibly prognosis of heart failure can be expected. It still remains to be seen whether other patient populations, like those with milder heart failure symptoms or those with ventricular arrhythmias in the absence of clinical heart failure, can benefit from cardiac resynchronization. Technological advancement in the delivery and lead system should make the procedure less time consuming. This, together with an effort to reduce costs of cardiac resynchronization devices should enable more patients with heart failure to benefit from this sophisticated technology.

Questions regarding the role of CRT in patients with right bundle branch block, patients with significant mitral insufficiency, and patients with pacing indications in general (should everybody get a BV device?) are still awaiting answers from clinical trials. The key to the future cost-effective use of CRT will be a better understanding of patient selection to ensure maximal benefit.

## Summary

CRT offers today another option for some patients with heart failure, side by side with more "traditional" therapies like drugs, assist devices, and heart transplantation. Clinical studies show that in properly selected patients a significant improvement in hemodynamic parameters and clinical status can be achieved by BV pacing. It is still unknown whether this type of therapy will also result in a survival benefit for patients with severe heart failure. The next few years certainly promise to be as exciting for CRT as were the last few.

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